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# Prognostic Value of Exercise Right Ventricular-Pulmonary Arterial Coupling in Primary Mitral Regurgitation


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**Short title: TAPSE/sPAP in Primary Mitral Regurgitation**

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**Abstract: (346 words)**

**Background:** Managing significant primary mitral regurgitation (PMR) is challenging. Right ventricular-pulmonary arterial coupling (RV-PAc), assessed via tricuspid annular plane systolic excursion (TAPSE) and systolic pulmonary artery pressure (sPAP) ratio, reflects RV adaptability to afterload. This international multi-center cohort study aimed to evaluate the prognostic value of rest and exercise TAPSE/sPAP (exTAPSE/sPAP) in PMR.

**Methods:** Between January 2019 and December 2023, 211 patients (derivation cohort, 64±12 years, 40% women) and 146 patients (validation cohort, 66 ±13 years, 39% women) with moderate or severe PMR, no or discordant symptoms and without left ventricular systolic dysfunction or atrial fibrillation (AF) underwent semi-supine cycle-ergometry cardiopulmonary exercise testing combined with exercise echocardiography. TAPSE/sPAP was measured at rest, intermediate (defined as the first ventilatory threshold) and peak exercise. The primary endpoint was the composite of cardiovascular death, unplanned cardiovascular hospitalizations and new AF.

**Results:** In the derivation cohort, 48 patients reached the composite outcome (median follow-up 24 months (QR [12-51]). Intermediate and peak exTAPSE/sPAP were strongly correlated (r=0.84, p <0.001), with intermediate exTAPSE/sPAP offering superior feasibility (98% versus 92%) with comparable prognostic accuracy to peak exTAPSE/sPAP [AUC 0.794 (0.730-0.849) versus 0.765 (0.698-0.823)] and therefore was used as the exercise TAPSE/sPAP parameter. Patients with a reduced rest TAPSE/sPAP (cut-off 0.8mm/mmHg) and intermediate exTAPSE/sPAP (cut-off 0.6mm/mmHg) had a lower event-free survival (log-rank p<0.0001). Intermediate exTAPSE/sPAP and percent-predicted peak $VO_2$ were independently associated with the primary endpoint [HR=0.64 (0.51-0.80), per 0.1mm/mmHg increase (p <0.001) and HR=2.03 (1.05-3.93), if <80%

(p=0.04), respectively] and had incremental prognostic value beyond age, left atrial volume index, MR severity, rest TAPSE/sPAP and mitral valve intervention (time-dependent covariable). Similar results were found when rest and intermediate exTAPSE/sPAP were included in the multivariable model as categorical parameters. Validation in an independent cohort confirmed the consistent and robust performance of both multivariable models, irrespective of whether TAPSE/sPAP was modeled as a continuous or categorical variable.

**Conclusions:** Exercise RV-PAc, particularly intermediate exTAPSE/sPAP, is a robust and feasible parameter, independently associated with adverse outcomes. It provides prognostic information beyond resting variables and cardiorespiratory fitness, potentially refining risk stratification and guiding management in patients with PMR.

**Keywords:** • RV PA coupling • TAPSE/sPAP • Primary mitral regurgitation • Exercise echocardiography • Cardiopulmonary exercise test

**Nonstandard Abbreviations and Acronyms**

3D-RVEF — Three-dimensional RV ejection fraction

CRF — Cardiorespiratory fitness

CPET — Cardiopulmonary exercise testing

CPETecho — Cardiopulmonary exercise testing with simultaneous echocardiography

CVH —cardiovascular hospitalizations

exPHT — Exercise pulmonary hypertension

exTAPSE/sPAP — Exercise TAPSE/sPAP

MVR — Mitral valve replacement/repair

MR — Mitral regurgitation

MVP — Mitral valve prolapse

mPAP/CO slope — Mean pulmonary artery pressure/cardiac output slope

PMR — Primary mitral regurgitation

RER — Respiratory exchange ratio

RV-PAc — Right ventricular to pulmonary arterial coupling

RVFAC — RV fractional area change

RVFWS — RV free wall strain

RVGLS — RV global longitudinal strain

TR — Tricuspid regurgitation

$VO_2$ — Peak oxygen uptake

## Clinical Perspective

### What Is New?

- In patients with at least moderate primary mitral regurgitation, without class I indication for intervention, exercise tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio (exTAPSE/sPAP) and percent-predicted peak $VO_2$ were independently associated with cardiovascular death, unplanned cardiovascular hospitalizations and new atrial fibrillation.
- exTAPSE/sPAP, particularly at intermediate level, is a robust and feasible parameter, independently associated with adverse outcomes, outperforming mean pulmonary artery pressure/cardiac output slope.
- Adding intermediate exTAPSE/sPAP and percent-predicted peak $VO_2$ incrementally improved risk stratification beyond baseline parameters (age, left atrial volume indexed, mitral regurgitation severity, and rest TAPSE/sPAP).

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### What Are the Clinical Implications?

- Combined exercise echocardiography and respiratory gas analysis provides prognostic information in patients with at least moderate primary mitral regurgitation without a class I indication for intervention.
- Patients with at least moderate primary mitral regurgitation and presenting with decreased intermediate exTAPSE/sPAP and reduced cardiorespiratory fitness (defined by percent-predicted peak $VO_2$ <80%) should be monitored more closely and may potentially require earlier intervention.

## Introduction

Mitral regurgitation (MR) is the second-most frequent valvular heart disease in Europe.[1] Optimal management of patients with significant primary mitral regurgitation (PMR) who have no or discordant symptoms remains controversial. Exercise echocardiography has been proposed as an additional test for this subset of patients, offering valuable prognostic information by assessing changes in MR volume and pulmonary pressures during peak exercise.[2-3]

The most recent ESC guidelines have introduced the concept of exercise pulmonary hypertension (exPHT), defined as mean pulmonary artery pressure (mPAP) >30 mmHg and mean pulmonary artery pressure/cardiac output slope (mPAP/CO slope) >3 mmHg/L/min rather than a single systolic pulmonary artery pressure (sPAP) value at peak exercise.[4,5] However, assessing exPHT without considering the right ventricular (RV) function has limitations, as it overlooks the interplay between RV load and performance.[6] RV to pulmonary arterial coupling (RV-PAc) has been introduced to quantify the RV's adaptation to its afterload and to detect impending RV failure.[7-9] In clinical practice, it is frequently assessed non-invasively using the ratio of tricuspid annular plane systolic excursion (TAPSE) to sPAP.[7-10] The prognostic value of RV-PAc was recently shown in patients with heart failure,[7-13] PH[9,14] and/or valvular heart disease.[15-20] However, there are no studies evaluating the potential prognostic role of rest and exercise TAPSE/sPAP (exTAPSE/sPAP) in patients with significant PMR who are asymptomatic or exhibit discordant symptoms.

We aimed to characterize RV-PAc defined by TAPSE/sPAP at rest and exercise, in patients with significant PMR, without left ventricle (LV) systolic dysfunction/dilatation or history of permanent/persistent atrial fibrillation (AF). We hypothesized that rest and

exTAPSE/sPAP are associated with clinical outcomes and that exTAPSE/sPAP provides superior prognostic information compared to resting parameters. Furthermore, we aimed to compare the prognostic value of exTAPSE/sPAP to that of mPAP/CO slope.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study population

### Derivation Cohort

In this cohort study, we prospectively assessed for eligibility 260 consecutive patients with at least moderate chronic PMR, either asymptomatic (severe) or presenting with symptoms (moderate), referred for cardiopulmonary exercise testing (CPET) with simultaneous echocardiography (CPETecho) at three tertiary hospital centers in Belgium (Jesse Hospital, Oost Limburg Hospital, and Sint-Jan Bruges Hospital) between October 2016 and March 2024. Patients were excluded if they had a class I indication for intervention, such as LV ejection fraction (LVEF) ≤60% and/or LV end-systolic diameter (LVESD) ≥40mm;[2,3] more than mild concomitant valvular disease, including mitral stenosis, history of permanent /persistent AF or congenital heart disease causing ExPHT. All patients underwent spirometry before CPETecho. Patients with more than moderate airflow obstruction (i.e., forced expiratory volume in 1s [FEV1] / forced vital capacity [FVC] <0.70 and FEV1<50% of predicted FEV1) and/or restrictive pattern (<80% of predicted FVC) were excluded – **Figure S1**. As previously described, this protocol is part of a standardized workup in a dedicated valvular heart disease clinic.[21] All patients underwent a thorough evaluation encompassing blood testing, 12-lead electrocardiogram, spirometry, and clinical examination. The local ethical committees approved the study protocol (Hasselt, Belgium; No. B2432020000038B). This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

**Validation Cohort.**

We prospectively assessed for eligibility 187 consecutive patients with at least moderate chronic PMR, asymptomatic or with discordant symptoms, referred for CPETecho at Pisa University Hospital (Italy) between September 2020 and December 2023. The same exclusion criteria used in the derivation cohort were applied (**Figure S1**). This protocol is part of a standardized workup in a dedicated dyspnea clinic.[22] The Local Ethics Committee approved the protocol (number 19204). All study subjects provided written informed consent before evaluation in the dyspnea clinic.

**Cardiopulmonary Exercise Test Combined with Exercise Stress Echocardiography**

***Respiratory Gas Analysis***

Patients performed a maximal, symptom-limited, semi-supine cycle-ergometer test (Cardiovit CS-200 Ergospiro, Schiller [Baar, Switzerland], and Ergoline ergoselect 1200 GmbH [Germany]), according to a standardized CPETecho protocol. After conducting a comprehensive transthoracic echocardiography (TTE) at rest, an individualized ramp protocol was selected to achieve a total exercise duration between 8 and 12 minutes. At intermediate exercise, defined by achieving the first ventilatory threshold, we acquired the second set of TTE images. The ramp protocol continued until exhaustion, with a third acquisition of TTE images just before peak exercise, usually defined by a respiratory exchange ratio (RER) >1.05, unless limiting or high-risk features occurred, as previously described.[21] Patients were encouraged to reach maximal exertion (RER >1.10). Cardiorespiratory fitness (CRF) was assessed by peak oxygen uptake ($VO_2$), expressed as either an absolute value or a percentage of the predictive value derived from the Wasserman formula.[23] Reduced CRF was defined as percent-predicted peak $VO_2$ <80%. The oxygen

pulse and the slope of minute ventilation to carbon dioxide production ($VE/VCO_2$ slope) were also collected.

***Echocardiography***

Experienced sonographers acquired a standardized set of echocardiographic images at rest, intermediate and peak exercise. All analyses were performed offline on EchoPAC in the derivation cohort (V.203, General Electric Healthcare, Chicago, IL, United States) and on TomTec in the validation cohort (TomTec Imaging Systems, Unterschleissheim, Germany), in accordance with current recommendations.[24,25]

MR severity was determined using a multiparametric approach, combining quantitative and qualitative methods. Quantitative assessment included the proximal isovelocity surface area (PISA) method to calculate effective regurgitant orifice area (EROA) and regurgitant volume. Volumetric methods were used to cross-validate regurgitant volume through differences in stroke volume (SV) between the left ventricular outflow tract and mitral inflow. Qualitative parameters (color Doppler jet size, flow convergence, and pulmonary vein systolic flow reversal) were also considered, ensuring a comprehensive assessment.[26] MR mechanism was categorized according to the Carpentier classification.[26] Chamber volumes and LVEF were calculated with the modified Simpson method. Left atrium (LA) and LV strain were measured according to current recommendations.[27,28] SV was calculated by multiplying the LV outflow tract (LVOT) area by the LV outflow tract velocity-time integral. Cardiac output (CO) was obtained by multiplying SV by heart rate. sPAP was determined by summing the tricuspid regurgitation (TR) gradient, calculated from peak transvalvular tricuspid velocity, and the semiquantitatively estimated right atrial pressure (RAP). TR envelope was enhanced by the routine administration of agitated colloid

(Gelofusine 4%, Braun, Melsungen, Germany) at rest and intermediate and peak exercise to maximize feasibility and reproducibility, as previously described **(Figure S2).**[21] The mPAP was calculated based on sPAP using the Chemla equation. The mPAP/CO slope was calculated by linear regression through three data points (mPAP and CO at rest, intermediate and peak exercise), as previously validated.[29]

RV systolic function was assessed by the percentage RV fractional area change (RVFAC).[25] RV free wall S', TAPSE, RV global longitudinal strain (RVGLS) and RV free wall strain (RVFWS) were measured from the RV-focused apical view using commercially available software and according to current recommendations.[24-25,28] RV-PAc was assessed non-invasively as TAPSE/sPAP ratio at rest and exercise. Three-dimensional RV ejection fraction (3D-RVEF) using 3D echocardiography was available in the validation cohort and performed according to current guidelines (Supplemental Material)**.**[30]

**Event-Free Survival**

Patients were followed up until October 30, 2024. Follow-up information was collected by reviewing patient charts. We defined a combined endpoint, including cardiovascular death, unplanned cardiovascular hospitalizations (CVH) and new-onset AF, regardless of whether the patient underwent mitral valve replacement/repair (MVR). The occurrence of mitral valve intervention was entered as a time-dependent covariable but was excluded from the composite endpoint to avoid intervention bias. The patient's primary physician independently determined the clinical management of the patient.

**Statistical Analysis**

Normal distribution of continuous variables was assessed with Shapiro-Wilk test. Continuous variables were expressed as mean±SD or median [IQR] when not normally distributed. The independent samples Student's t-test and Mann–Whitney U test were used to compare groups. Categorical data were expressed as counts and percentages and compared with Pearson's chi-squared or Fisher's exact test when appropriate. All calculations were performed with software SPSS version 19 (SPSS Inc., Chicago, Illinois) and Medcalc (MedCalc Software Ltd, Ostend, Belgium).

**Derivation Cohort**

Survival analysis using a stepwise algorithm was conducted using the Cox proportional hazards regression model to evaluate multivariable-adjusted associations and time-to-event endpoints. The proportional hazards assumption for Cox regression was tested using Schoenfeld residuals. Continuous variables were tested for linearity on the log hazard scale, and no transformations were required. Missing values were <5% for all variables and were handled using complete case analysis. Sensitivity analyses using multiple imputation yielded consistent results and are available upon request. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

**Model 1** included age, left atrium indexed volume (LAVi), MR grade (severe versus moderate) and rest TAPSE/sPAP (continuous), with MVR included as a time-dependent covariable. Model 1 was expanded by incorporating percent-predicted peak $VO_2$ (<80% or ≥80%) – **Model 2**; and exTAPSE/sPAP (continuous) – **Model 3**. **Model 4**, in which exTAPSE/sPAP was substituted with mPAP/CO slope, was developed as a comparator for the accuracy of Model 3 in being associated with the combined endpoint. Sensitivity

analyses using Model 3 were performed in which unplanned CVH in the primary endpoint were restricted to hospitalizations due to heart failure, AF, and stroke (to account for potentially under-recognized AF) and with new AF events restricted to those occurring before the intervention (as AF after the intervention could bias the result).

Multivariable logistic regression analyses were also conducted to evaluate model performance through goodness-of-fit tests and area under the curve (AUC) across models. The Hanley–McNeil method was used to calculate the standard error of AUC, and the DeLong test to compare differences in AUC. Variables with a p-value $<0.05$ in univariable analysis were considered for inclusion in Models 3 and 4, provided they remained independently associated with the combined endpoint and significantly improved the AUC of the model. The assumptions for the logistic regression were met. All continuous independent variables were linearly related to the logit of the dependent variable, according to the Box-Tidwell procedure. Multicollinearity was evaluated by confirming no significant correlation between independent variables ($r <0.70$) and a variance inflation factor $<5$.

In the derivation cohort, a receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value for rest and exTAPSE/sPAP associated with the combined endpoint, defined as the values maximizing the sum of sensitivity and specificity Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. For clinical translation, categorized rest and exTAPSE/sPAP values were incorporated into the final multivariable model, replacing their continuous counterparts. Model performance across Models 1 to 3 with rest and exTAPSE/sPAP as categorical variables was assessed through goodness-of-fit tests and by comparison of AUC values across models using multivariable logistic regression analyses.

**Validation Cohort**

The probability equation derived from the logistic regression of Model 3 in the derivation cohort, incorporating rest and exTAPSE/sPAP as either continuous or categorical variables, was applied to estimate individual risk in the validation cohort. Classification tables were used to evaluate the accuracy of the logistic regression models from the derivation cohort, applying the criterion value corresponding to the Youden index J derived from the ROC curve analysis of the models in the derivation cohort.

## RESULTS

### Study Population

A total of 211 patients (derivation cohort: 40% female, mean age 64 ± 12 years) and 146 patients (validation cohort: 39% female, mean age 66 ± 13 years) were eligible for the study **(Figure S1**). Age, sex, comorbidities and NT-proBNP were similarly distributed between cohorts (**Table 1**). Mitral Regurgitation International Database Quantitative (MIDA-Q) Mortality Risk Score, a previously validated score predicting long-term survival in patients with mitral valve prolapse (MVP),[31] was assessed. Most patients had an intermediate MIDA-Q Mortality Risk Score with no differences between derivation and validation cohorts and no high-risk scores observed (maximum score of 7).

### Echocardiographic Characteristics

MVP/flail was the predominant etiology (96% and 91% in the derivation and validation cohorts, respectively. The remaining patients were classified as Carpentier type IIIa: 8 patients in the derivation cohort (2 cases of rheumatic origin and 6 cases secondary to post-radiotherapy); 13 patients in the validation cohort (5 cases of rheumatic origin and 8 cases secondary to post-radiotherapy).

The proportion of patients with severe MR was higher in the validation cohort (55% versus 43%, p=0.03), with a significantly higher median EROA and regurgitant volume (**Table 2**). Indexed LV end-diastolic volume and LAVi were higher in the validation cohort, but LV systolic function and LA strain were similar in both groups. RV function parameters were within the normal range and similar between cohorts at rest and exercise, except for rest S' and global longitudinal and free wall strains, which were significantly higher in the validation cohort (**Tables 2 and 3**). Conversely, rest and exercise sPAP were significantly

higher in the validation cohort, leading to significantly lower rest and exTAPSE/sPAP in this group, aligning with a higher proportion of patients with severe MR in the validation cohort, which is associated with increased pulmonary pressures. The mPAP/CO slope was similar in both groups.

**CPET Characteristics**

There were no significant differences between the two cohorts in peak RER, peak workload, and peak $VO_2$, with approximately half of the patients achieving < 80% of predicted peak VO2 (43% versus 47%, p=0.46) (**Table 4**). $VE/VCO_2$ slope and percent-predicted $FEV_1$ were higher in the validation cohort. There were no significant differences in other CPET parameters.

**Clinical Outcomes**

In the derivation cohort, 48 patients (23%) reached the composite outcome during a median follow-up of 24 months (IQR [12-51]): 2 patients died (due to ruptured aortic aneurysm and heart failure, respectively); 32 were hospitalized due to cardiovascular causes (78% due to heart failure, AF or stroke) and 33 patients had new AF episodes. The event-free survival rate was 78% and 62% at 1 and 2 years of follow-up. During follow-up, 73 patients (59% men, 64±13 years) in the derivation cohort underwent MVR (92% repair procedures) due to the development of symptoms (81%), unplanned CVH due to AF or heart failure (12%) or new onset AF without the need for hospitalization (4%).

**Comparison of Patients With and Without Events**

Patients with the composite endpoint (Group A; n=48) were older and had a higher LAVi, with lower atrial reservoir strain than those without the composite endpoint (group B; n=163; **Table S1**). Global LV longitudinal strain, peak exercise S', rest and exercise TAPSE were lower in group A, while other parameters of LV and RV systolic function did not differ. TAPSE and CO were higher in group B, whereas pulmonary pressures were lower in this group (**Table S1**), leading to significantly higher rest and exTAPSE/sPAP and a higher mPAP/CO slope in group B. Of note, MR classification (Carpentier type II versus Carpentier type IIIa) and type of degenerative mitral valve disease (Barlow's disease versus FED) were not significantly associated with the primary endpoint.

**Baseline Prognostic Model (Model 1)**

In a baseline model (**Model 1**) including age, LAVi, MR severity, rest TAPSE/sPAP (continuous variable) and MVR as a time-dependent covariable, rest TAPSE/sPAP (HR 0.83 (0.73-0.96), per 0.1mm/mmHg increase, p <0.01) was independently associated with the primary endpoint, alongside MVR (**Table S2)**.

**Intermediate versus Peak exTAPSE/sPAP: feasibility and accuracy**

Intermediate exTAPSE/sPAP was measured at the first ventilatory threshold, corresponding to a mean workload of 49 ± 24 watts and a mean RER of 0.95 ± 0.09.

Contrary to rest, intermediate exTAPSE/sPAP demonstrated a significantly higher prognostic accuracy than its individual components: AUC=0.794 (0.730-0.849) versus AUC=0.701 (0.631-0.765), p=0.01, for intermediate exercise sPAP and AUC=0.794 (0.730-0.849) versus AUC=0.712 (0.643-0.776), p=0.04, for intermediate exercise TAPSE.

Absolute TAPSE/sPAP values at exercise were more strongly associated with outcome than their respective changes from rest [AUC=0.794 (0.730-0.849) versus 0.525 (0.454-0.595), p <0.001 for intermediate exercise and AUC=0.765 (0.698-0.823) versus 0.592 (0.519-0.662), p <0.001 for peak exercise], supporting the use of intermediate (and peak) exTAPSE/sPAP as a single prognostic parameter, independent of resting or dynamic changes.

Intermediate exTAPSE/sPAP demonstrated comparable prognostic accuracy to peak exTAPSE/sPAP (AUC=0.794 (0.730-0.849)] versus AUC=0.765 (0.698-0.823), p=0.24) but with better feasibility (98% versus 92%) due to more technical issues when measuring RV-PAc at peak exercise. Additionally, intermediate and peak exTAPSE/sPAP were strongly correlated (r=0.84, p <0.001), supporting the concept that intermediate exercise measurements effectively represent peak RV-PA coupling capacity while minimizing technical limitations at higher exercise stages. Therefore, intermediate exTAPSE/sPAP was chosen as the exercise RV-PAc parameter to integrate Model 3.

**Intermediate exTAPSE/sPAP: feasibility across exercise capacities**

The feasibility of intermediate exTAPSE/sPAP remained high and without significant differences between patients with maximal or submaximal exercise test (RER>1.05 versus RER≤1.05) – 98% versus 95%, p=0.28, respectively – and among patients with a maximal exercise test and normal versus decreased percent-predicted peak $VO_2$: 97% versus 100%, p=0.20, respectively. Overall, these findings suggest that exercise tolerance does not affect the feasibility of intermediate exTAPSE/sPAP. Intermediate exTAPSE/sPAP remained independently associated with outcome in patients with a maximal exercise (RER>1.05)

and decreased percent-predicted peak $VO_2$ (<80%): adjusted HR 0.69 (0.50-0.95), p=0.02. Therefore, intermediate exTAPSE/sPAP is clinically applicable even in patients with impaired exercise capacity but adequate effort, reinforcing the robustness of our findings.

**Incremental Prognostic Value of Exercise Parameters (Model 2 and 3)**

Adding percent-predicted peak $VO_2$ (<80% versus ≥80%) and intermediate exTAPSE/sPAP as a continuous variable (**Model 3)** significantly improved the prognostic accuracy of Model 1 in the derivation and validation cohorts (**Figure S3** and **Figure 1**, respectively). Age, MVR, percent-predicted peak $VO_2$ and intermediate exTAPSE/sPAP remained significantly associated with outcome: HR 1.03 (1.01-1.07), p=0.04; HR 3.37 (1.58-7.17), p <0.001; HR 2.03 (1.05-3.93), p <0.05 and HR 0.64 (0.52-0.80), per 0.1mm/mmHg increase, p <0.001, respectively (**Figure 1**).

Among the variables statistically significant in the univariable analysis, only LA reservoir strain remained independently associated with outcome when added to Model 3 (HR 0.92 (0.86-0.99), p <0.05), together with intermediate exTAPSE/sPAP and MVR, although not significantly changing the overall AUC of the final model (**Figure S4**). Finally, 3D-RVEF, available in the validation cohort, was overall preserved, with mean values of 60.3±7.1%. In the multivariable Cox regression analysis, 3D-RVEF was not independently associated with the primary endpoint (HR 0.99 (0.80-1.22), p=0.79) and did not show incremental prognostic value (**Figure S5**).

**Sensitivity Analysis**

When unplanned CVH were restricted to HF, AF, and stroke in Model 3, intermediate exTAPSE/sPAP and percentage-predicted peak VO  remained significantly associated with the outcome: HR 0.71 (0.56-0.91) per 0.1mm/mmHg increase, p <0.01 and HR 2.10 (1.04-4.25), p <0.05. When new AF in the composite endpoint was restricted to new AF events occurring before the intervention, intermediate exTAPSE/sPAP also remained independently associated with outcome (HR 0.65 (0.52-0.83), per 0.1mm/mmHg increase, p <0.01). To evaluate whether comorbidities influenced the development of new AF, we restricted the composite endpoint to new-onset AF and individually added common risk factors (obesity, hypertension, dyslipidemia, smoking status, diabetes, and coronary artery disease) to the final multivariable Model 3. None of these comorbidities were independently associated with the endpoint, suggesting that new AF was driven by hemodynamic and structural cardiac parameters rather than systemic comorbidities. In patients with moderate PMR, intermediate exTAPSE/sPAP also remained significantly associated with the primary endpoint (HR 0.61, (0.42-0.88), per 0.1mm/mmHg increase, p <0.01), even when unplanned CVH in the primary endpoint was restricted to heart failure, AF and stroke hospitalizations (HR 0.69 (0.48-0.99), per 0.1mm/mmHg increase, p <0.05).

Finally, replacing intermediate exTAPSE/sPAP with peak exTAPSE/sPAP in Model 3 did not change the overall prognostic accuracy of the model [AUC 0.781 (0.716-0.837) for the model incorporating peak exTAPSE/sPAP, p=0.31].

**Intermediate exTAPSE/sPAP versus mPAP/CO slope**

To assess the relative performance of Model 3, Model 4 was developed by substituting intermediate exTAPSE/sPAP with the mPAP/CO slope (both as continuous variables), allowing comparison of their respective associations with the combined endpoint. The accuracy of Model 1 was significantly refined by adding mPAP/CO slope and percent-predicted peak $VO_2$ (likelihood $\chi 2=29.5$, $p < 0.05$), but the accuracy of Model 3 was significantly higher than that of Model 4 (AUC 0.815 (0.754-0.866) versus 0.746 (0.681-0.805), p=0.02; **Figure S6**). Of note, when mPAP/CO slope was categorized (<3 mmHg/L/min versus ≥3 mmHg/L/min) it was independently associated with outcome in Model 3, alongside rest TAPSE/sPAP (HR 2.23 (1.14-4.36), p=0.02 and HR 0.87 (0.76-0.99), per 0.1mm/mmHg increase, p=0.04, respectively).

Among the variables statistically significant in the univariable analysis, only LA reservoir strain remained independently associated with outcome when added to Model 4 (HR 0.93 (0.88-0.99), p <0.05), together with rest TAPSE/sPAP and MVR, although not significantly changing the overall AUC of the final model, similarly to Model 3 (**Figure S7**).

**Clinical Applicability: Rest and intermediate exTAPSE/sPAP as categorical variables**

For improved clinical applicability, rest and intermediate exTAPSE/sPAP were categorized according to the optimal cut-off value associated with the combined endpoint.

Patients with a reduced rest TAPSE/sPAP (optimal cut-off point 0.8mm/mmHg) and intermediate exTAPSE/sPAP (optimal cut-off point 0.6 mm/mmHg) had a lower event-free survival (log-rank p <0.0001, **Figure 2)**.

Categorized rest and intermediate exTAPSE/sPAP were incorporated in Model 3, replacing their corresponding continuous counterparts. As shown in **Figure 3,** percent-predicted peak

$VO_2$ and intermediate exTAPSE/sPAP remained significantly associated with outcome in the derivation cohort [OR 2.34 (1.01-5.40), p=0.04 if <80%, OR 7.91 (3.11-20.16), p <0.001, if <0.6mm/mmHg, respectively) and significantly improved accuracy of the model in the validation cohort [AUC 0.618 (0.536-0.696) versus 0.804 (0.732-0.864), p=0.003].

We also show that the accuracy of the previously validated MIDA-Q Mortality Risk Score is significantly improved by adding rest TAPSE/sPAP (<0.8 mm/mmHg versus ≥0.8 mm/mmHg), percent-predicted peak $VO_2$ (<80% versus ≥80%) and intermediate exTAPSE/sPAP (<0.6 mm/mmHg versus ≥0.6 mm/mmHg), with percent-predicted peak $VO_2$ and intermediate exTAPSE/sPAP remaining independently associated with the primary endpoint **(Figure S8)**. Furthermore, the accuracy of Model 3 is significantly higher compared to the MIDA-Q Mortality Risk Score in derivation and validation cohorts– **Figure S9**.

**Validation Cohort Outcomes and Accuracy**

In the validation cohort, 45 patients (31%) reached the composite outcome during follow-up (20 months IQR [8-44]: 4 cardiovascular deaths (due to heart failure worsening), 20 unplanned CVH and 34 new AF episodes. The event-free survival rate was 73% and 60% at 1 and 2 years of follow-up. The accuracy determined by analysis of the logistic regression coefficients for the composite outcome from the derivation data set in the validation cohort was 73% (61% sensitivity and 84% specificity) for Model 3, with rest and intermediate exTAPSE/sPAP as continuous variables (**Table S3)**; 75% (63% sensitivity and 87% specificity) for Model 3, with rest and intermediate exTAPSE/sPAP as categorical

variables (**Table S4)** and 69% (64% sensitivity and 74% specificity) for Model 4 (**Table S5**).

**Figure 4** presents a concise summary of the study's key results.

## Discussion

This study demonstrates that RV-PAc at intermediate exercise provides significant prognostic information beyond resting parameters in patients with PMR who are considered not to be at high risk of adverse events according to current guidelines.[2,3] All included patients had preserved RV systolic function at rest and sPAP ≤50 mmHg in more than 97% of cases. These findings highlight the importance of evaluating dynamic RV adaptability to pressure load during exercise, even in ostensibly low-risk patients.

### Interpretation of Key Findings

Patients with lower TAPSE/sPAP ratios, particularly at intermediate exercise, experienced higher rates of adverse events. Intermediate exTAPSE/sPAP was strongly associated with the combined endpoint and demonstrated similar prognostic accuracy to peak exercise. Importantly, intermediate exTAPSE/sPAP remained feasible even in patients with reduced exercise tolerance, broadening its clinical utility. Because this parameter combines RV contractility (TAPSE) with afterload (sPAP), it is a marker of RV-PA interaction. Furthermore, TAPSE/sPAP is derived from standard M-mode and continuous-wave Doppler measurements and is not vendor-dependent, increasing reproducibility.

Significant MR initially leads to LA and LV dilatation as compensatory adaptations to volume overload.[32] These structural changes are often asymptomatic but eventually progress to elevated LA and LV filling pressures, pulmonary hypertension, and RV dysfunction.[32] Previous studies have shown that pulmonary vascular involvement and RV dysfunction are associated with increased mortality in PMR.[33-36] A recently proposed staging

system based on extra-valvular cardiac damage confirms a stepwise increase in mortality risk, with the most pronounced risk observed in patients with RV involvement.[37,38]

By capturing the RV's ability to adapt to rising pulmonary pressures, TAPSE/sPAP offers a non-invasive and sensitive measure of pulmonary vascular and RV dysfunction. In our study, RV function parameters were thoroughly assessed. Rest 3D-RVEF was available in the validation cohort but did not demonstrate an independent prognostic value. This may be due to the overall preserved RV function in our population and the technical limitations of 3D imaging, particularly during exercise.[30] It is conceivable that 3D-RVEF may have greater utility in patients with secondary tricuspid regurgitation,[39] that were excluded from this analysis.

Our findings expand upon earlier work by Coisne and Messika-Zeitoun, who demonstrated the prognostic value of peak VO and exercise pulmonary hypertension in asymptomatic PMR.[40,41] The prognostic value of RV function and sPAP during exercise in patients with severe MR has been previously reported: Kusunose et al. identified TAPSE <19mm immediately after treadmill testing as an independent predictor of valve surgery-free survival[42] and Coisne et al. highlighted the prognostic value of exercise pulmonary hypertension (SPAP ≥ 55mmHg at 25W) and reduced aerobic capacity (peak VO <80%).[40] We build on this by integrating CPET with stress echocardiography in a single protocol. This combined CPETecho approach captures both ventilatory and hemodynamic responses and provides a more comprehensive risk assessment.

Compared with prior work by Doldi et al., who showed that rest TAPSE/sPAP predicted outcomes in symptomatic PMR patients undergoing transcatheter repair,[43] we now demonstrate the value of this marker in a broader, asymptomatic population. Our findings

show that rest TAPSE/sPAP adds independent and incremental prognostic information after adjusting for age, LA volume, and MR severity, which are parameters incorporated in the MIDA-Q Mortality Risk Score.[31] Furthermore, we show that adding rest TAPSE/sPAP, intermediate exTAPSE/sPAP, and percent-predicted peak VO  significantly improves the accuracy of the MIDA-Q score. Notably, intermediate exTAPSE/sPAP (<0.6 mm/mmHg) and percent-predicted peak VO  remained independently associated with outcomes, reinforcing the added value of dynamic RV-PAc assessment.

Interestingly, rest TAPSE/sPAP remained an independent predictor even when adjusting for other exercise-derived metrics such as mPAP/CO slope and LA reservoir strain. This underscores its physiological relevance. While mPAP/CO slope reflects total pulmonary resistance, it does not incorporate RV function directly. As such, rest RV-PAc complements exercise-derived indices and may serve as a marker of early dysfunction.

The optimal cut-off for rest TAPSE/sPAP in our study (0.8 mm/mmHg) is higher than that reported by Doldi et al. (0.3 mm/mmHg),[43] reflecting differences in patient populations: asymptomatic patients without intervention indication and preserved RV function in our study versus symptomatic, high-risk patients in theirs. Notably, our rest and intermediate exTAPSE/sPAP thresholds closely align with lower normal limits reported in healthy populations.[9]

A major strength of our study is the exclusion of mitral interventions from the composite endpoint to avoid clinician-driven bias. However, to account for the confounding effect of intervention timing, we incorporated MVR as a time-dependent covariable in all multivariable models. This adjustment confirms that the prognostic value of intermediate exTAPSE/sPAP is independent of procedural intervention and further validates its role as a

reliable, clinically meaningful marker. Another strength of our work is the significant heterogeneity of rest TAPSE/sPAP between the validation and derivation cohorts, mainly driven by higher sPAP values, aligning with a higher proportion of patients with severe MR in the validation cohort. Therefore, we show that the prognostic value of intermediate exTAPSE/sPAP and percent-predicted peak VO is robust across a broader spectrum of PMR severity and enhances the generalizability and clinical applicability of our findings to real-world patient populations.

**Limitations and Future Directions**

Excluding patients with Class I indication for surgery or with persistent or permanent AF, may limit generalizability to more advanced cases or restrict the applicability of findings to real-world, heterogeneous populations. Future studies should validate these results in broader cohorts, including patients with varied PMR etiologies and risk profiles. Data on race and ethnicity were not systematically recorded and could not be included in the analysis, limiting insights into potential disparities in RV–PA coupling or prognostic response.

While peak and intermediate exTAPSE/sPAP were measurable in over 90% of patients, echocardiographic limitations (poor tricuspid regurgitation signal quality, inter-operator variability and low feasibility of accurately estimating exercise RAP) remain challenges.[44-46] We maximized feasibility and accuracy by using agitated Gelofusine to enhance the Doppler signal, consistent with evidence from Claessen et al., who demonstrated a high correlation with invasive measurements using this technique.[47] Conversely, we show and externally validate the independent prognostic value of exTAPSE/sPAP as a continuous variable, accounting for variability and highlighting its robustness.

Although our study validates the prognostic utility of RV-PAc during exercise, it does not address whether CPETecho-guided management improves outcomes over standard surveillance. Importantly, TAPSE/sPAP values were not disclosed in clinical reports and did not influence treatment decisions, strengthening the internal validity of our analysis. Future research should investigate the potential of CPETecho-guided intervention strategies to optimize timing and improve long-term outcomes in PMR.

## Conclusion

This study establishes RV-PA coupling during exercise as a valuable prognostic tool in patients with moderate and severe primary mitral regurgitation, especially those with discordant symptoms. Intermediate exTAPSE/sPAP emerges as a robust, non-invasive, and feasible marker that enhances current risk stratification. Integrating this parameter into clinical practice could enable earlier identification of patients at risk and support more personalized management strategies.

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**Supplemental Material**

Supplemental Methods

Tables S1–S5

Figures S1-S9

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**Figure Legends**

**Figure 1.** Prognostic value of RV-PAc (rest and intermediate exTAPSE/sPAP modelled as continuous variables) and cardiopulmonary exercise testing parameters in PMR.

**Panel A:** Multivariable Cox regression analysis of the combined endpoint (cardiovascular death, unplanned cardiovascular hospitalization and new atrial fibrillation) in the derivation cohort, using Model 3, which includes MVR as a time-dependent covariable .

**Panel B:** Incremental prognostic value of percent-predicted peak VO (Model 2) and intermediate exTAPSE/sPAP (Model 3), based on stepwise increases in model fit ($\chi^2$) in the validation cohort.

**Panel C:** ROC curves and AUC comparison showing improved discriminatory performance from Model 1 (age, LAVi, MR severity, and rest TAPSE/sPAP), to Model 2 (adding percent-predicted peak VO ), and Model 3 (adding intermediate exTAPSE/sPAP), in the validation cohort.

**Abbreviations:**

LAVi – Left atrial volume indexed; MVR – Mitral valve replacement/repair; MR – Mitral regurgitation; TAPSE – Tricuspid annular plane systolic excursion; sPAP – Pulmonary artery systolic pressure; $VO_2$ – Oxygen uptake.

**Figure 2.** Kaplan-Meier survival curves stratified according to rest TAPSE/sPAP (optimal cut-off point of 0.8 mm/mmHg) and intermediate exTAPSE/sPAP (optimal cut-off point of 0.6 mm/mmHg).

**Panel A:** Kaplan-Meier curves at 36 months of follow-up for the probability of freedom from cardiovascular death, unplanned cardiovascular hospitalization and new atrial fibrillation, according to rest TAPSE/sPAP (optimal cut-off point of 0.8 mm/mmHg).

**Panel B:** Kaplan-Meier curves at 36 months of follow-up for the probability of freedom from cardiovascular death, unplanned cardiovascular hospitalization and new atrial fibrillation, according to intermediate exTAPSE/sPAP (optimal cut-off point of 0.6 mm/mmHg).

**Figure 3.** Prognostic value of RV-PAc (rest and intermediate exTAPSE/sPAP modelled as categorical variables) and cardiopulmonary exercise testing parameters in PMR.

**Panel A:** Binominal logistic regression analysis of the combined endpoint (cardiovascular death, unplanned cardiovascular hospitalization and new atrial fibrillation) in the derivation cohort, using Model 3.

**Panel B:** Incremental prognostic value of percent-predicted peak VO (Model 2) and intermediate exTAPSE/sPAP <0.6 versus ≥0.6mm/mmHg (Model 3), based on stepwise increases in model fit ($\chi^2$) in the validation cohort.

**Panel C:** ROC curves and AUC comparison showing improved discriminatory performance from Model 1 (age, LAVi, MR severity, and rest TAPSE/sPAP <0.8 versus ≥0.8mm/mmHg), to Model 2 (adding percent-predicted peak VO ), and Model 3 (adding intermediate exTAPSE/sPAP <0.6 versus ≥0.6mm/mmHg), in the validation cohort.

**Abbreviations:**

LAVi – Left atrial volume indexed; MR – Mitral regurgitation; TAPSE – Tricuspid annular plane systolic excursion; sPAP – Pulmonary artery systolic pressure; $VO_2$ – Oxygen uptake.

**Figure 4. Summary of the study's key results.** The top-left panel shows outcomes for patients with PMR (≥ moderate), no or discordant symptoms, and preserved ejection fraction (>60%) in the derivation cohort; the bottom-left panel shows the same for the validation cohort. Exercise RV-PAc, measured as TAPSE/sPAP, quantifies the adaptation of

the RV to its afterload. Lower TAPSE/sPAP ratios at intermediate exercise in patients with at least moderate PMR are associated with higher risk of cardiovascular death, unplanned CVH and new AF. The top right panel depicts Kaplan-Meier curves over 36 months showing freedom from the combined endpoint, stratified by intermediate-exercise TAPSE/sPAP (optimal threshold 0.6 mm/mmHg) in the derivation cohort. The bottom right panel shows the corresponding adjusted HR for intermediate exercise TAPSE/sPAP in the derivation cohort and the accuracy of the final multivariable model in the validation cohort.

**Abbreviations:**

CVH —cardiovascular hospitalizations; HR — Hazard ratio; PMR — Primary mitral regurgitation; RV — Right ventricular; RV-PAc — Right ventricular to pulmonary arterial coupling; TAPSE – Tricuspid annular plane systolic excursion; sPAP – Pulmonary artery systolic pressure.

**Tables**

**Table 1.** Study sample baseline characteristics.

| | Derivation cohort (Belgium, n=211) | Validation cohort (Italy, n=146) | p value |
|---|---|---|---|
| **Demographics** | | | |
| Age, years | 64 ± 12 | 66 ±13 | 0.14 |
| Female, n (%) | 84 (40) | 57 (39) | 0.85 |
| BMI, kg/m$^2$ | 25 ± 3 | 24 ±4 | 0.08 |
| BSA, m$^2$ | 1.9 ± 0.2 | 1.8 ±0.3 | 0.06 |
| SBP at rest, mmHg | 144 ± 21 | 133 ± 19 | **<0.001** |
| DBP at rest, mmHg | 82 ± 13 | 80 ±11 | 0.13 |
| **Biochemical profile** | | | |
| NT-proBNP, ng/L | 160 [74 – 340] | 173 [81 – 381] | 0.09 |
| Creatinine clearance (CKD-EPI), mL/min | 78 ± 20 | 76 ± 24 | 0.39 |
| Haemoglobin, g/dL | 13.8 ± 1.5 | 13.5 ± 1.5 | 0.07 |
| **Comorbidities** | | | |
| Hypertension, n (%) | 111 (53) | 79 (54) | 0.85 |
| Dyslipidemia, n (%) | 86 (41) | 58 (40) | 0.86 |
| Smoker, n (%) | 42 (20) | 29 (20) | 0.99 |
| Diabetes, n (%) | 11 (5) | 13 (9) | 0.14 |
| Coronary artery disease, n (%) | 18 (9) | 6 (4) | 0.07 |
| **Medication** | | | |

| | | | |
|---|---|---|---|
| ACEI or ARBs | 65 (31) | 70 (45) | **0.01** |
| Beta-blockers | 74 (35) | 53 (36) | 0.85 |
| DHP Calcium channel blockers | 7 (3) | 16 (11) | **0.01** |
| Loop diuretics | 9 (4) | 2 (3) | 0.62 |
| MRA | 18 (9) | 16 (11) | 0.53 |
| Statins | 70 (33) | 55 (38) | 0.33 |
| Nitrates | 4 (2) | 2 (3) | 0.55 |
| MIDA-Q Mortality Risk Score | 5 [2 – 6] | 5 [2 – 7] | 0.77 |

Data are expressed as mean and standard deviation, median and interquartile range or absolute and relative frequency, as appropriate.

**Abbreviations:**

ACEI – Angiotensin-converting-enzyme inhibitors; ARBs – Angiotensin receptor blockers; BMI – Body mass index; BSA – Body surface area; DBP – Diastolic blood pressure; DHP – Dihydropyridine; MIDA-Q – Mitral Regurgitation International Database Quantitative; MRA – Mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro–B-type natriuretic peptide; SBP – Systolic blood pressure

**Table 2.** Echocardiographic characteristics at rest.

| | Derivation cohort (Belgium, n=211) | Validation cohort (Italy, n=146) | p value |
|---|---|---|---|
| **MR severity** | | | |
| MR grading severity | | | |
| Moderate, n (%) | 121 (57) | 66 (45) | **0.03** |
| Severe, n (%) | 90 (43) | 80 (55) | |
| Effective regurgitant orifice area, $mm^2$ | 40 [30 - 50] | 44 [30 - 68] | **0.01** |
| Regurgitant volume, mL | 60 [44 - 70] | 64 [53 - 81] | **0.01** |
| **Left ventricle and left atrium morphology** | | | |
| IVS, mm | 10 ± 2 | 11 ± 2 | **0.03** |
| LVEDD, mm | 51 ± 7 | 52 ± 7 | 0.19 |
| PWT, mm | 9 ± 2 | 9 ± 1 | 0.99 |
| LVMi, $g/m^2$ | 98 ± 31 | 112 ± 34 | **0.01** |
| LVEDVi, $mL/m^2$ | 70 ± 20 | 75 ± 25 | **0.04** |
| LVESVi, $mL/m^2$ | 24 ± 8 | 26 ± 10 | 0.06 |
| LAVi, $mL/m^2$ | 41 ± 18 | 46 ± 18 | **0.02** |
| LAVi≥60 mL/ $m^2$, n (%) | 28 (13) | 24 (16) | 0.43 |
| LA reservoir strain, % | 22 ± 7* | 24 ± 10 | 0.06 |
| LA conduit strain, % | 12 ± 5* | 13 ± 6 | 0.09 |
| LA booster strain, % | 10 ± 4* | 11 ± 6 | 0.07 |
| **Left ventricular systolic and diastolic function** | | | |
| LV ejection fraction, % | 65 ± 4 | 66 ± 5 | 0.07 |

| | | | |
|---|---|---|---|
| LV global longitudinal strain, % | 19 ± 2 | 19 ± 3 | 0.99 |
| SV at rest, ml | 70 ± 19 | 63 ± 21 | **0.01** |
| Heart rate at rest, bpm | 71 ± 13 | 76 ±14 | **<0.001** |
| CO at rest, L/min | 4.9 ± 1.4 | 4.5 ± 1.6 | 0.06 |
| CI at rest, L/min/$m^2$ | 2.6 ± 0.7 | 2.5 ± 0.5 | 0.14 |
| E/A | 1.4 ± 0.6 | 1.4 ± 1.0 | 0.99 |
| Septal e', cm/s | 8 ± 2 | 9 ± 3 | **0.02** |
| Septal E/e' | 12 ± 5 | 11 ± 5 | 0.07 |
| **Right ventricle function and pulmonary hemodynamic** | | | |
| RVFAC at rest, % | 49 ± 9 | 51 ± 10 | 0.06 |
| RVFAC rest >35%, n (%) | 211 (100) | 143 (98) | 0.06 |
| TAPSE at rest, mm | 24 ± 4 | 23 ± 3 | 0.06 |
| RV global longitudinal strain, % | 20 ± 3 | 24 ± 5 | **<0.001** |
| RV free wall strain, % | 24 ± 5 | 27 ± 8 | **<0.001** |
| RV free wall S' rest, cm/s | 12 ± 2 | 14 ± 3 | **<0.001** |
| sPAP at rest, mmHg | 24 ± 6 | 30 ± 10 | **<0.001** |
| sPAP >50mmHg at rest, n (%) | 1 (1) | 4 (3) | 0.17 |
| TAPSE/sPAP ratio at rest, mm/mmHg | 1.04 ± 0.29 | 0.74 ± 0.23 | **<0.001** |

Data are expressed as mean and standard deviation, median and interquartile range or absolute and relative frequency, as appropriate.

*available in 188 patients in the derivation cohort.

**Abbreviations:**

CI – Cardiac index; CO – Cardiac output; IVS – Interventricular septum; LA – Left atrium; LAVi – Left atrial volume indexed; LV – Left ventricle; LVEDD – Left ventricular end-diastolic diameter; LVEDVi – Left ventricular end-diastolic volume indexed; LVESVi – Left ventricular end-systolic volume indexed; LVMi – Left ventricular mass indexed; MR – Mitral regurgitation; PWT – Posterior wall thickness; RV – Right ventricle; RVFAC – Right ventricle fractional area change; sPAP – Pulmonary artery systolic pressure; SV – Stroke volume; TAPSE – Tricuspid annular plane systolic excursion.

**Table 3.** Echocardiographic characteristics during exercise.

| | Derivation cohort (Belgium, n=211) | Validation cohort (Italy, n=146) | p value |
|---|---|---|---|
| **Right ventricle function and pulmonary hemodynamics** | | | |
| TAPSE at intermediate exercise, mm | 28 ± 4 | 27 ± 7 | 0.09 |
| TAPSE at peak exercise, mm | 29 ± 5 | 28 ± 4 | 0.06 |
| RV free wall S' intermediate exercise, cm/s | 14 ± 3 | 15 ±4 | 0.06 |
| RV free wall S' peak exercise, cm/s | 16 ± 4 | 17 ± 4 | 0.06 |
| sPAP at intermediate exercise, mmHg | 40 ± 9 | 47 ± 15 | **<0.001** |
| sPAP at peak exercise, mmHg | 50 ± 10 | 55 ± 15 | **<0.001** |
| TAPSE/sPAP ratio at intermediate exercise, mm/mmHg | 0.73 ± 0.21 | 0.60 ± 0.20 | **<0.001** |
| TAPSE/ sPAP ratio at peak exercise, mm/mmHg | 0.60 ± 0.15 | 0.57 ± 0.19 | 0.09 |
| mPAP/CO slope, mmHg/L/min | 2.3 [1.8 – 3.2] | 2.3 [1.9 – 3.4] | 0.81 |
| **Cardiac Output** | | | |
| SV at intermediate exercise, ml | 88 ± 24 | 70 ± 22 | **<0.001** |
| SV at peak exercise, ml | 90 ± 24 | 79 ± 25 | **<0.001** |
| Heart rate at intermediate exercise, bpm | 99 ± 16 | 92 ± 18 | **<0.001** |
| Heart rate at peak exercise, bpm | 131 ± 22 | 120 ± 27 | **<0.001** |
| CO at intermediate exercise, L/min | 8.6 ± 2.2 | 7.3 ± 2.3 | **<0.001** |
| CO at peak exercise, L/min | 11.7 ± 3.3 | 10.7 ± 3.6 | **0.02** |
| CI at intermediate exercise, L/min/$m^2$ | 4.6 ± 1.1 | 4.2 ± 1.9 | **0.03** |

| | | | |
|---|---|---|---|
| CI at peak exercise, L/min/$m^2$ | 6.3 ± 1.6 | 5.9 ± 1.8 | 0.05 |

**Abbreviations:**

CO – Cardiac output; CI – Cardiac Index; mPAP – Mean pulmonary artery pressure; RV – Right ventricle; sPAP – Pulmonary artery systolic pressure; TAPSE – Tricuspid annular plane systolic excursion

**Table 4.** Cardiopulmonary exercise test variables.

| | Derivation cohort (Belgium, n=211) | Validation cohort (Italy, n=146) | p value |
|---|---|---|---|
| **CPET variables** | | | |
| $FEV_1$ predicted, % | 86 ± 17 | 91 ±20 | **0.04** |
| FVC, L | 3.2 ± 1.0 | 3.3 ± 1.1 | 0.38 |
| RER at peak exercise | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.99 |
| Peak $VO_2$, mL/kg/min | 20 ± 6 | 19 ± 5 | 0.15 |
| Percent-predicted peak $VO_2$, % | 85 ± 23 | 82 ± 16 | 0.18 |
| Percent-predicted peak $VO_2$ <80%, n (%) | 91 (43) | 69 (47) | 0.46 |
| $P_{ETCO2}$ at peak exercise, mm Hg | 37 ± 5 | 36 ± 7 | 0.13 |
| $EqCO_2$ minimal | 29 ± 4 | 30 ± 6 | 0.07 |
| $VE/VCO_2$ slope | 29 ± 6 | 31 ± 8 | **0.03** |
| VE at peak exercise, L | 56 ± 17 | 53 ± 17 | 0.13 |
| VT at peak exercise, L | 1.79 ± 0.56 | 1.74 ± 0.55 | 0.51 |
| VE/MVV | 0.56 ± 0.15 | 0.54 ± 0.17 | 0.08 |
| Workload at peak exercise, Watt | 111 ± 47 | 108 ±43 | 0.55 |

**Abbreviations:**

$EqCO_2$ – Ventilatory equivalent of carbon dioxide; $FEV_1$ – forced expiratory volume in the first second; FVC – Forced vital capacity; $P_{ETCO2}$ – Partial pressure of endtidal $CO_2$; RER –

Respiratory exchange ratio; VE – Minute ventilation; $VO_2$ – Maximal Oxygen Uptake; VT – Tidal Volume; MVV – Maximal voluntary ventilation